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(54) Title: TREATMENT OF MOOD DISORDERS WITH A GROWTH HORMONE SECRETAGOGUE

(57) Abstract

A growth hormone secretagogue is useful, alone or in combination with antidepressants, for the prevention or the treatment of mood disorders, in particular depression.

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TITLE OF THE INVENTION
TREATMENT OF MOOD DISORDERS WITH A GROWTH HORMONE SECRETAGOGUE

BACKGROUND OF THE INVENTION

Mood disorders (or affective disorders) are psychopathologic states in which a disturbance of mood is either a primary determinant or constitutes the core manifestation. These conditions, especially the depressive forms, are heterogeneous and common in both psychiatry and general medicine. Mood disorders include the syndromes of major depression and mania (bipolar manic-depressive illness) and are characterized by changes in mood as the primary clinical manifestation. They commonly include disordered autonomic functioning and behavior, as well as persistent abnormalities of mood and increased risk of self-harm or suicide.

Such disorders include: mood disorders, such as depression or depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder. Bipolar disorder includes both mania and depression, or only mania. Bipolar disorder has been further divided into bipolar I disorder and bipolar II disorder. In the case of bipolar I disorder, there is the presence of a full-blown manic episode, and the case of bipolar II disorder, there is mild hypomania only.

Numerous compounds are known in the art to be useful for the prevention and treatment of mood disorders such as depression, including e.g., heterocyclic antidepressants, lithium salts, monamine oxidase inhibitors, serotonin uptake inhibitors, and the like.

Nevertheless, these threapeutic regimens suffer from numerous problems, including potential for addiction, lack of alertness, impairment of memory, interaction with other medication, etc. Accordingly, a more physiological way to treat depression would be highly desirable.

It is known that changes in neurotransmission which occur in major depressive illnesses may also affect the neuroregulation of various hormones, such as cortisol, prolactin, melatonin and growth hormone. Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. Although the effects of growth hormone on the central nervous system are poorly understood, the known effects of growth hormone on anabolic processes could contribute to an improved sense of well-being. This is unlikely, however, because patients receiving growth hormone treatment reported improvements in level of psychological functioning before changes in their body composition and exercise performance were evident (e.g. Sartorio, et al., Clinical Physiology, 14, 527-537 (1994)).

A deficiency in growth hormone secretion can result in various medical disorders, depending on the age of onset. In children, the syndrome is characterized by short stature with normal body proportions and reduced growth rate (dwarfism). A deficiency in growth hormone secretion in adult life may be characterized by excessive adiposity, reduced muscle mass, impaired exercise capacity, reduced body water, decreased bone mineral density, and psychological disorders. The physiological impariment in patients with growth hormone deficiency is similar to that in patients suffering from endogenous depression in which the function of the monaminergic neurons has been found to be disturbed.

A dysfunction in the neurosecretion of growth hormone is observed in major depressive illness that is characterized by reduced growth hormone pulsitility (Fiasche, et al., Psychoneuroendocrinology, 20(7), 727-733 (1995)). In addition, recurrent depression is associated with a reduction in sleep-related growth hormone secretion (Franz, et al., Biol. Psychiatry, 38, 720-729 (1995)). An impaired ability to secrete adequate amounts of growth hormone at the normal time after sleep onset may be a factor in the

pathology of depression. In patients with growth hormone deficiency who were treated with recombinant growth hormone, the cerebrospinal fluid levels of the dopamine metabolite homovanillic acid and thyroid hormone T4 were reported to be similar to the levels seen after successful treatment of depressive disorders with antidepressant drugs (Burman, et al., Clinical Endocrinol., 44, 319-324 (1996)), but this study failed to examine the psychological profile or mental state of the patients (McGauley, Clinical Endocrinol., 44, 325-326 (1996)).

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known growth hormone secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF, IGF-I or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray. In addition, administration of exogenous growth hormone may result in side-effects, including edema, and does not correlate with the pulsitile release seen in the endogenous release of growth hormone.

Certain compounds have been developed which stimulate the release of endogenous growth hormone. Peptides which are known to

stimulate the release of endogenous growth hormone include growth hormone releasing hormone, the growth hormone releasing peptides GHRP-6 and GHRP-1 (described in U.S. Patent No. 4,411,890, PCT Patent Pub. No. WO 89/07110, and PCT Patent Pub. No. WO 89/07111) and GHRP-2 (described in PCT Patent Pub. No. WO 93/04081), as well as hexarelin (J. Endocrinol Invest., 15(Suppl 4), 45 (1992)). Other compounds possessing growth hormone secretagogue activity are disclosed in the following: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; PCT Patent Pub. No. WO 96/05195; PCT Patent Pub. No. WO 96/15148; PCT Patent Pub. No. WO 96/22782; PCT Patent Pub. No. WO 96/22997; PCT Patent Pub. No. WO 96/24580; PCT Patent Pub. No. WO 96/24587; PCT Patent Pub. No. WO 96/35713; PCT Patent Pub. No. WO 96/38471; PCT Patent Pub. No. WO 97/00894; PCT Patent Pub. No. WO 97/06803; PCT Patent Pub. No. WO 97/07117; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995). Additional compounds with growth hormone secretagogue activity are described herein.

SUMMARY OF THE INVENTION

The present invention is directed to the use of a compound which has the ability to stimulate or amplify the release of natural or endogenous growth hormone for the prevention and treatment of mood disorders, in particular depression, in a warm-blooded animal. The advantage of this method is that in contrast to injections of growth hormone it provides a physiological-like pulsatile profile of growth hormone release from the pituitary gland. Accordingly, the present invention provides a method for the prevention and treatment of mood disorders including depression in a warm-blooded animal comprising the administration of a growth hormone secretagogue. The present invention further provides a pharmaceutical composition for the prevention and treatment of mood disorders, including depression.

DESCRIPTION OF THE INVENTION

The present invention is directed to the use of a compound which has the ability to stimulate or amplify the release of natural or endogenous growth hormone for the prevention and treatment of mood disorders, in particular depression, in a warm-blooded animal. In particular, the present invention provides a method for the prevention and treatment of mood disorders such as depression in a warm-blooded animal comprising the administration of a growth hormone secretagogue.

The following clinical targets may be addressed with the present invention: affective disorder, mood disorder, depression, bipolar manic-depressive illness, psychosis, enuresis, deficit hyperactivity disorder, anxiety disorders, post-tramautic stress disorder, panic disorder, obsessive-compulsive disorder, bulimia nervosa, anorexia nervosa, chronic pain disorder including diabetic and other peripheral neuropathic syndromes, fibromyalgia, peptic ulcer, irritable bowel syndrome, chronic fatigue, cataplexy, migraine, and the like. The present invention is further directed to a method for ameliorating a state of depression in a mammal which comprises administering an effective amount of a growth hormone secretagogue

In the present invention, it is preferred that the subject mammal is a human. Although the present invention is applicable both old and young people, it may find greater application in elderly people.

By the term "growth hormone secretagogue" is meant any exogenously administered compound or agent that directly or indirectly stimulates or increases the endogenous release of growth hormone, growth hormone-releasing hormone or somatostatin in an animal, in particular, a human.

The growth hormone secretagogue may be peptidal or non-peptidal in nature, however, the use of a orally active growth hormone secretagogue is preferred. In addition, it is preferred that the growth hormone secretagogue induce or amplify a pulsatile release of endogenous growth hormone. It is also preferred that the growth hormone secretagogue be able to cause the release of growth hormone at night or during the sleep cycle, especially in the first half of the night or of the sleep cycle, and even more especially in the first few hours following sleep onset, or alternatively in the period immediately preceding sleep onset.

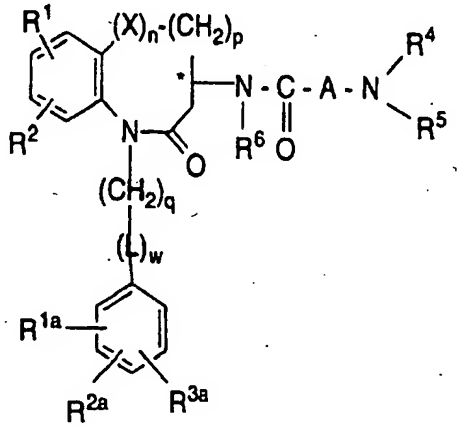
The growth hormone secretagogue may be used alone or in combination with other growth hormone secretagogues or with other agents which are known to be beneficial in the prevention or treatment of mood disorders, especially depression. The growth hormone secretagogue and the other agent may be coadministered, either in concomitant therapy or in a fixed combination. For example, the growth hormone secretagogue may be administered in combination with other compounds which are known in the art to be useful for the prevention and treatment of mood disorders such as depression, including e.g., heterocyclic antidepressants, lithium salts, monamine oxidase inhibitors, serotonin uptake inhibitors, serotonin reuptake inhibitors, and the like, such as: adatanserin, adinazolam, alaproclate, aletamine, alpidem, alprazolam, amedalin, amitriptyline, amoxapine, aptazapine, azaloxan, azepindole, azipramine, binospirone, bipenamol, bretazenil, bupropion, busprione, butacetin, butriptyline, caroxazone, cartazolate, ciclazindol, cidoxepin, cilobamine, clodazon, clomipramine, clorazepate, clozapine,

cotinine, cyclindole, cypenamine, cyprolidol, cyproximide, daledalin, dapoxetine, dazadrol, dazepinil, desipramine, dexamisole, deximafen, diazepam, dibenzepin, dioxadrol, divalproex, dothiepin, doxepin, duloxetine, eclanamine, encyprate, etoperidone, fantridone, fenmetozole, fenmetramide, fazolamine, flesinoxan, fluotracen, fluvoxamine, fluoxetine, fluparoxan, gamfexine, glemanserin, guanoxyfen, hydroxyzine, imafen, imiloxan, imipramine, indeloxazine, intriptyline, iprindole, ipsapirone, isocarboxazid, ketipramine, lithium, lofepramine, lorazepam, lortalamine, maprotiline, melitracen, meprobamate, milacemide, minaprine, mirisetron, mirtazapine, moclobemide, modaline, napactadine, napamezole, nefazodone, nisoxetine, nitrafudam, nomifensine, nortriptyline, ocinaplon, octriptyline, ondansetron, opipramol, oxaprotiline, oxazepam, oxypertine, panadiplon, pancopride, paroxetine, pazinaclone, perphenazine, phenelzine, pirandamine, pizotyline, pridefine, prolintane, protriptyline, quipazine, rolicyprine, seproxetine, selegiline, serazapine, sertraline, sibutramine, sulpiride, suritozole, tametraline, tampramine, tandamine, tandospirone, thiazesim, thozalinone, tomoxetine, tranylcypromaine, trazodone, trebenzomine, trimipramine, venlafaxine, viloxazine, zalospirone, zimeldine, zometapine and the like, and salts thereof, as well as admixtures and combinations thereof, and other agents.

Representative growth hormone secretagogues are disclosed in: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 89/07110; PCT Patent Pub. No. WO 89/07111; PCT Patent Pub. No. WO 93/04081; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No.

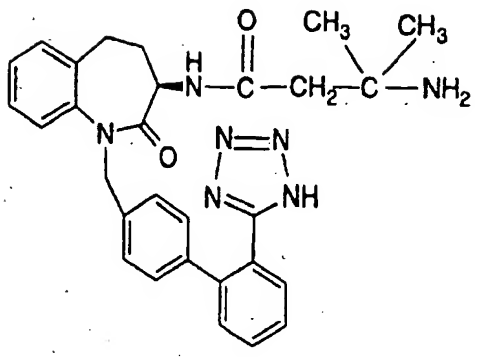
WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; PCT Patent Pub. No. WO 96/05195; PCT Patent Pub. No. WO 96/15148; PCT Patent Pub. No. WO 96/22782; PCT Patent Pub. No. WO 96/22997; PCT Patent Pub. No. WO 96/24580; PCT Patent Pub. No. WO 96/24587; PCT Patent Pub. No. WO 96/35713; PCT Patent Pub. No. WO 96/38471; PCT Patent Pub. No. WO 97/00894; PCT Patent Pub. No. WO 97/06803; PCT Patent Pub. No. WO 97/07117; J. Endocrinol Invest., 15(Suppl 4), 45 (1992)); Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

A representative first class of growth hormone secretagogues is set forth in U.S. Patent No. 5,206,235 as follows:

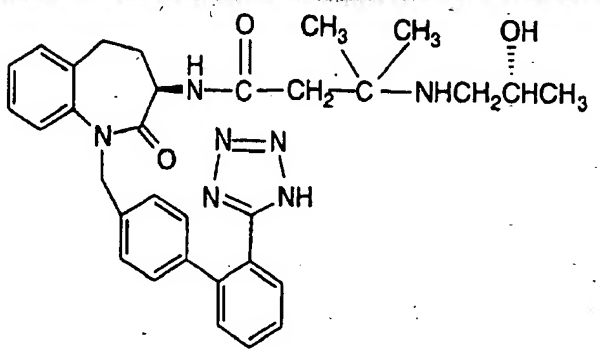


wherein the various substituents are as defined in U.S. Patent 5,206,235.

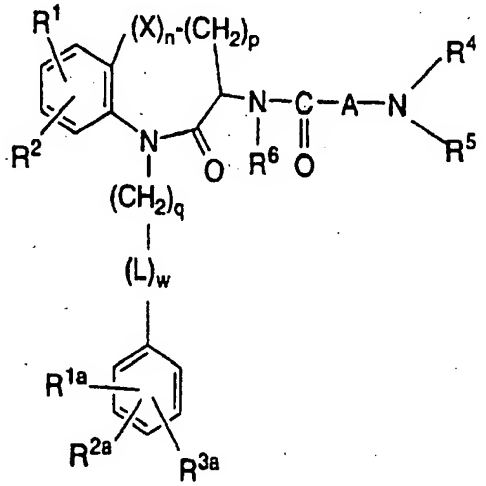
The most preferred compounds within this first class are identified as having the following structures:



or

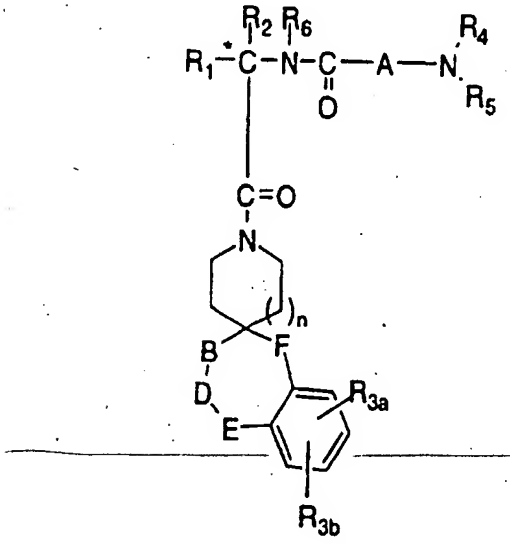


A representative second class of growth hormone secretagogues is set forth in U.S. Patent No. 5,283,241 and PCT Patent Publication No. 94/05634 as having the following structural formula:

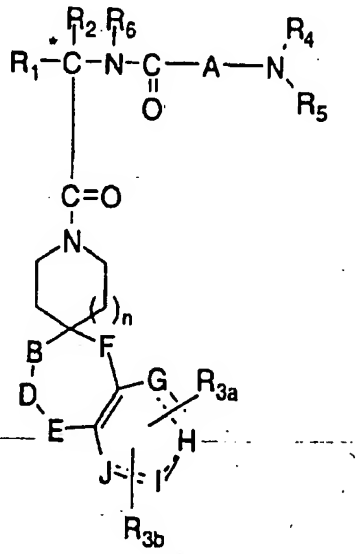


wherein the various substituents are as defined in U.S. Patent 5,283,241 and PCT Patent Publication No. 94/05634.

A representative third class of growth hormone secretagogues is disclosed in PCT Patent Pub. No. WO 94/13696 as compounds of the following structural Formulas I and II:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

$-C_1$-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

$-C_3$-C_7 cycloalkyl-(C_1-C_6alkyl), $-C_1$-C_5alkyl-K-C_1-C_5 alkyl, -aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

$-C_3$-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$, or $-C\equiv C-$,

and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro,

-$N(R_2)(R_2)$, -$N(R_2)C(O)R_2$, -$C(O)OR_2$, -$C(O)N(R_2)(R_2)$, -$SO_2N(R_2)(R_2)$, -$N(R_2)S(O)_2$ aryl, and -$N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:

hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

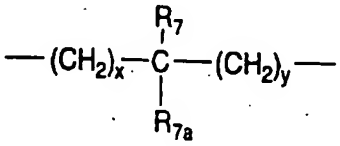
R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

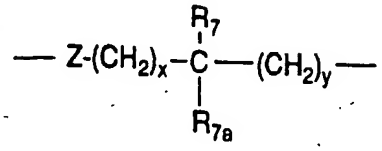
R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

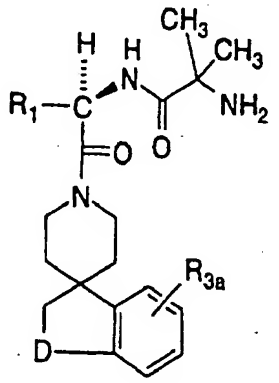
B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;
R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, -$(CH_2)_q$-aryl, -$(CH_2)_q$-$C(O)OR_2$, -$(CH_2)_q$-$C(O)O(CH_2)_q$-aryl, or -$(CH_2)_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -$C(O)OR_2$;

R_9 is selected from the group consisting of:
-R_2, -$(CH_2)_q$-aryl, -$C(O)R_2$, -$C(O)(CH_2)_q$-aryl, -SO_2R_2, -$SO_2(CH_2)_q$-aryl, -$C(O)N(R_2)(R_2)$, -$C(O)N(R_2)(CH_2)_q$-aryl, -$C(O)OR_2$, 1-H-tetrazol-5-yl, -SO_3H, -$SO_2NHC{\equiv}N$, -$SO_2N(R_2)$aryl, -$SO_2N(R_2)(R_2)$,
and wherein the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -$O(CH_2)_q$ aryl, 1 to 2 -$C(O)OR_{2a}$, 1 to 2 -$C(O)O(CH_2)_q$ aryl, 1

to 2 -C(O)N(R_{2a})(R_{2a}), 1 to 2 -C(O)N(R_{2a})(CH_2)$_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -C(O)NHSO_2R_{2a}, -S(O)$_m R_{2a}$, -C(O)NHSO_2(CH_2)q-aryl, -SO_2NHC≡N, -SO_2NHC(O)R_{2a}, -SO_2NHC(O)(CH_2)$_q$aryl, -N(R_2)C(O)N(R_{2a})(R_{2a}), -N(R_{2a})C(O)N(R_{2a})(CH_2)$_q$-aryl, -N(R_{2a})(R_{2a}), -N(R_{2a})C(O)R_{2a}, -N(R_{2a})C(O)(CH_2)q aryl, -OC(O)N(R_{2a})(R_{2a}), -OC(O)N(R_{2a})(CH_2)$_q$ aryl, -SO_2(CH_2)$_q$CONH-(CH_2)wNHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

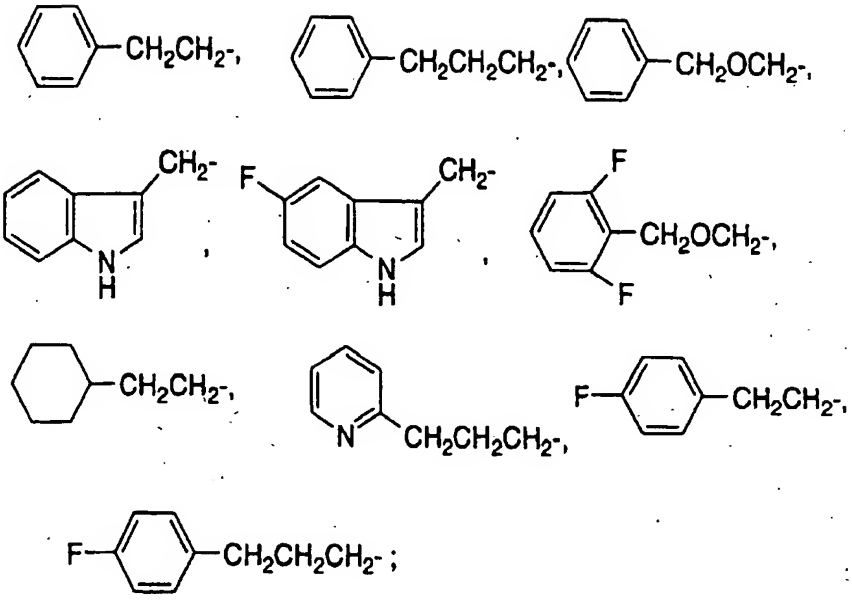
m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;
and pharmaceutically acceptable salts and individual diastereomers thereof.

Within this third class, the most preferred growth hormone secretagogues employed in the instant invention are realized in structural Formula V:



V

wherein R_1 is selected from the group consisting of:



R_{3a} is H, or fluoro;

D is is selected from the group consisting of:

-O-, -S-, -S(O)m-, N(R2), $NSO_2(R_2)$, $NSO_2(CH_2)$taryl, NC(O)(R2),

$NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $NSO_2(CH_2)_qC(O)$-N(R2)(R2),

$N\text{-}SO_2(CH_2)_qC(O)$-$N(R_2)(CH_2)_wOH$,